1 554 026

PATENT SPECIFICATION

(11) 1 554 026

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C2C 1175 1672 179X 200 213 215 220 225 226 22Y 247 253 25Y 28X 302 304 305 30Y 311 31Y 351 352 360 362 363 364 366 367 368 36Y 386 387 388 38Y 401 409 40Y 43X 491 509 50Y 623 624 625 628 633 635 652 658 662 672 67X 695 760 761 767 BJ TU
C2B 1
C3S 2 3A 3B 3D 5 7B 7D

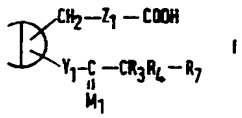
(19)

(54) PROSTAGLANDIN LACTONES

(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

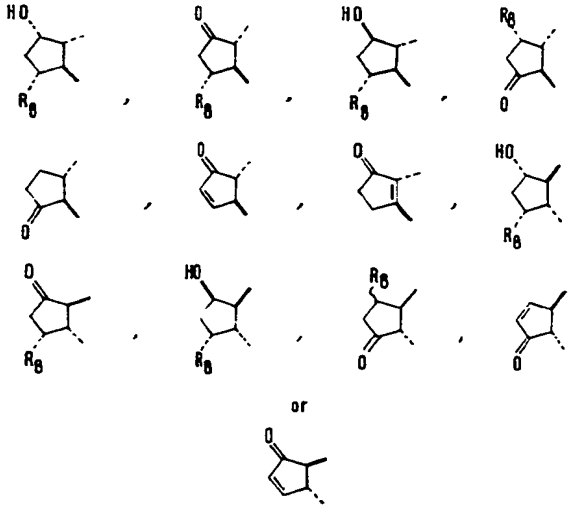
This invention relates to 1,15-lactones of known prostaglandins. Various prostaglandins, their esters, acylates and pharmacologically acceptable salts are extremely potent in causing various biological responses. For that reason, these compounds are useful for pharmacological purposes. See, for example, Bergstrom *et al.*, Pharmacol. Rev. 20, 1 (1968) and references cited therein.

Known prostaglandins include those of formula I



I

wherein D is

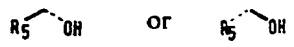


or

wherein R_8 is hydrogen or hydroxy;

wherein R_3 and R_4 are the same or different and are each hydrogen, methyl or fluorine, with the proviso that $—CR_3R_4—$ is not —CFMe—;

wherein M_1 is



wherein R_5 is hydrogen or methyl;

wherein R_7 is $—(CH_2)_m—CH_3$, wherein m is an integer of from one to 5, *cis*-CH=CH—CH_2CH_3, or an optionally substituted phenoxy or benzyl radical of the formula

wherein Z_3 is —O— or $—CH_2—$, T is chlorine, fluorine, trifluoromethyl or alkyl or alkoxy of one to 3 carbon atoms, s is zero, one, 2 or 3, with the proviso that the T's may be the same or different when s is 2 or 3, that not more than two T's are other than alkyl, and that Z_3 is not —O— when R_3 and/or R_4 is fluorine;

wherein Y_1 is *trans*-CH=CH—, $—CH_2CH_2—$, *cis*-CH=CH— or —C≡C—;

wherein n indicates attachment of the hydroxy group to the cyclopentane ring in either alpha or beta configuration; and

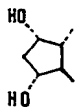
wherein Z_1 is

(1) *cis*-$CH=CH—CH_2—(CH_2)_g—CH_2—$,
(2) *cis*-$CH=CH—CH_2—(CH_2)_g—CF_2—$,
(3) *cis*-$CH_2—CH=CH—(CH_2)_g—CH_2—$,
(4) $—(CH_2)_3—(CH_2)_g—CH_2—$,
(5) $—(CH_2)_3—(CH_2)_g—(CF_2)_g—CH_2—$,
(6) $—CH_2—O—CH_2—(CH_2)_g—CH_2—$,
(7) $—L—O—(CH_2)_g—$ or
(8) $—L—CH_2—(CH_2)_g—$

wherein L is 1,3-phenylene and g is one, 2 or 3.

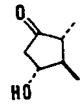
For the prostaglandin analogs described in formula I above, a convenient classification system according to cyclopentane ring structure is effected by referencing:

(a) PGF_α-type compounds when D is



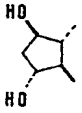
(b) 11-deoxy-PGF_α-type compounds when D is

(c) PGE-type compounds when D is

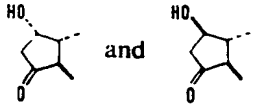


(d) 11-deoxy-PGE-type compounds when D is

(e) PGF_β-type compounds when D is

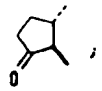


(f) PGD-type or 9β-PGD-type compounds, respectively, when $\mathcal{D}$ is



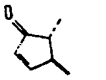
and ; and

(g) 9-deoxy-PGD-type compounds when $\mathcal{D}$ is



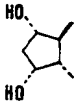
(h) 9-deoxy-9,10-didehydro-PGD-type compounds when $\mathcal{D}$ is

(i) PGA-type compounds when $\mathcal{D}$ is



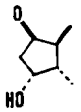
(j) PGB-type compounds when $\mathcal{D}$ is

(k) 8β,12α-PGF$_\alpha$-type compounds when $\mathcal{D}$ is



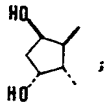
(l) 8β,12α,11-deoxy-PGF$_\alpha$-type compounds when $\mathcal{D}$ is

(m) 8β,12α-PGE-type compounds when $\mathcal{D}$ is

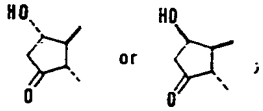


(n) 8β,12α-11-deoxy-PGE-type compounds when $\mathcal{D}$ is

(o) 8β,12α-PGF$_\beta$-type compounds when D is



(p) 8β,12α-PGD-type or 8β,9β,12α-PGD-type compounds, respectively, when D is



(q) 8β,12α-9-deoxy-PGD-type compounds when D is

(r) 8β,12α-9-deoxy-9,10-didehydro-PGD-type compounds when D is

and

(s) 8β12α-PGA-type compounds when D is

Those prostaglandin analogs wherein Z_1 is *cis*-CH=CH—CH_2—$(CH_2)_g$—CH_2— or *cis*-CH=CH—CH_2—$(CH_2)_g$—CF_2— are named as "PG_2" compounds. The latter compounds are further characterized as "2,2-difluoro" PG_2-type compounds. When g is 2 or 3, the prostaglandin analogs so described are "2a-homo" or "2a,2b-dihomo" compounds, since in this event the carboxy terminated side chain contains 8 or 9 carbon atoms, respectively, in place of the 7 carbon atoms contained in PGE_1. These additional carbon atoms are considered as though they were inserted between the C—2 and C—3 positions. Accordingly, these additional carbon atoms are referred to as C—2a and C—2b, counting from the C—2 to the C—3 position.

Further when Z_1 is —$(CH_2)_3$—$(CH_2)_g$—CH_2— or —$(CH_2)_3$—$(CH_2)_g$—CF_2, wherein g is as defined above, the PG analogs so described are "PG_1" compounds. When g is 2 or 3, the "2a-homo" and "2a,2b-dihomo" compounds are described as is discussed in the preceding paragraph.

When Z_1 is —CH_2—O—$CH_2(CH_2)_g$—CH_2— the PG analogs so described are named as "5-oxa-PG_1" compounds. When g is 2 or 3, the compounds so described are "2a-homo" or "2a,2b-dihomo" compounds, respectively, as discussed above.

When Z_1 is *cis*-CH_2—CH=CH—$(CH_2)_g$—CH_2—, wherein g is as defined above, the PG analogs so described are named "*cis*-4,5-didehydro-PG_1" compounds. When g is 2 or 3, the compounds so described are further characterized as "2a-homo" or "2a,2b-dihomo" compounds, respectively, as discussed above.

For the PG analogs wherein Z_1 is —L—O—$(CH_2)_g$— or —L—CH_2—$(CH_2)_g$— wherein L and g are as defined above, there are described, respectively, 3-oxa-3,7-inter-*m*-phenylene-4,5,6-trinor or 3,7-*inter*-*m*-phenylene-4,5,6-trinor-PG-type compounds, when g is one. When g is 2 or 3, the above compounds are additionally described as "2a-homo" or "2a,2b-dihomo" PG-type compounds, respectively.

The prostaglandin analogs of formula I in which Y is *cis*—CH=CH— are described as "13-*cis*" compounds.

Further when Y_1 is —C≡C— or —CH_2CH_2— the compounds so described are named as "13,14-didehydro" or "13,14-dihydro" compounds, respectively.

When R_7 is —$(CH_2)_m$—CH_3, wherein m is as defined above, the PG analogs so described are named as "19,20-dinor", "20-nor", "20-methyl", or "20-ethyl" compounds when m is one, 2, 4 or 5, respectively. When R_7 is optionally substituted benzyl as defined above, the PG analogs so described are named as "17-phenyl-18,19,20-trinor" compounds, when s is 0. When s is one, 2, or 3, the corresponding compounds are named as "17-(substituted phenyl)-18,19,20-trinor" compounds.

When R_7 is optionally substituted phenoxy as defined above, and neither R_3 nor R_4 is methyl, the PG analogs so described are named as "16-phenoxy-17,18,19,20-tetranor" compounds, when s is zero. When s is one, 2, or 3, the corresponding compounds are named as "16-(substituted phenoxy)-17,18,19,20-tetranor" compounds. When one and only one of R_3 and R_4 is methyl or both R_3 and R_4 are methyl, then the corresponding compounds wherein R_7 is as defined in this paragraph are named as "16-phenoxy or 16-(substituted phenoxy)-18,19,20-trinor" compounds or "16-methyl-16-phenoxy or 16-(substituted phenoxy)-18,19,20-trinor" compounds, respectively.

When R_7 is *cis*-CH=CH—CH_2CH_3, the compounds so described are "PG_3" or "*cis*-17,18-didehydro" compounds depending on whether Z_1 is *cis*-CH=CH—$(CH_2)_6$—CH_2— or *cis*-CH=CH—$(CH_2)_6$—CF_2—.

When at least one of R_3 and R_4 is not hydrogen then (except for the 16-phenoxy compounds discussed above) there are described the "16-methyl" (one and only one of R_3 and R_4 is methyl), "16,16-dimethyl" (R_3 and R_4 are both methyl), "16-fluoro" (one and only one of R_3 and R_4 is fluorine), and "16,16-difluoro" (R_3 and R_4 are both fluorine) compounds. For those compounds wherein R_3 and R_4 are different, the prostaglandin analogues so represented contain an asymmetric carbon atom at C—16. Accordingly, two epemeric configurations are possible: "(16*S*)" and "(16*R*)". Further, there is described by this invention the C—16 epimeric mixture: "(16*RS*)".

When Y_1 is *cis*-CH=CH— the compounds of this invention are *cis*-13-PG compounds. The convention used in this specification for representing such compounds is explained in our Application No. 26180/76 (Serial No. 1554024).

cis-13-PG-type compounds as drawn herein which have an hydroxy at C—15 in the alpha configuration are of the opposite relative stereochemical configuration at C—15 as that of *cis*-13-PGE_1, and are therefore named as "15-*epi*" compounds. When the beta hydroxy configuration is present, no special designation of this stereochemistry is provided.

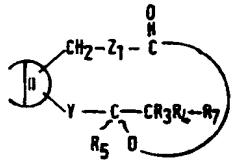
When Y_1 is *trans*-C=CH—, —CH_2CH_2— or —C≡C—, the same stereochemical configuration is intended as for PGE_1 as obtained from mammalian tissues unless the opposite stereochemical configuration at C—15 is indicated by the description "15-*epi*" i.e. 15β-hydroxy compounds.

The prostaglandin analogues of formula I can all be used for the purposes known for the basic prostaglandins from which they are derived. They are known to be capable of administration in various ways for various purposes: e.g., intravenously, intramuscularly, subcutaneously, orally, intravaginally, rectally, buccally, sublingually, topically, and in the form of sterile implants for prolonged acton. For intravenous injection or infusion, sterile aqueous isotonic solutions are known to be preferred. For subcutaneous or intramuscular injection, sterile solutions or suspensions are used. Tablets, capsules, and liquid preparations such as syrups, elixirs, and simple solutions, with the usual pharmaceutical carriers are used for oral sublingual administration. For rectal or vaginal administration, suppositories prepared as known in the art are used. For tissue implants, the use of sterile tablets or silicone rubber capsules or other objects containing or impregnated with the substance is known.

Methods for the preparation of large ringed lactones are known in the art. See, for example, E. J. Corey *et al.*, Journal of the Americal Chemical Society 96: 5614 (1974). Further, certain 1,9-lactones of cyclopentane containing carboxylic acids are known in the art. See South African Patent Application No. 737,357, Derwent Farmdoc CPI No. 28414V, which discloses 1,9-lactones of ω-heterocyclic prostaglandin analogs; Japanese Patent Application No. 0037—793, Derwent Farmdoc CPI No. 61147W, which discloses 15-deoxy-15-methyl-$PGF_{2\alpha}$, 1,9-lactone; and E. J. Corey *et al.*, Journal of the American Chemical Society 97: 653 (1975), which discloses $PGF_{2\alpha}$ 1,9-lactone. Further, the latter reference additionally discloses $PGF_{2\alpha}$ 1,15-lactone.

Finally, see Japanese Patent Application No. 50013—385, Derwent Farmdoc CPI No. 56267W, which discloses the 1,9-lactones of $PGF_{2\alpha}$ and (15*RS*)-15-methyl-$PGF_{2\alpha}$.

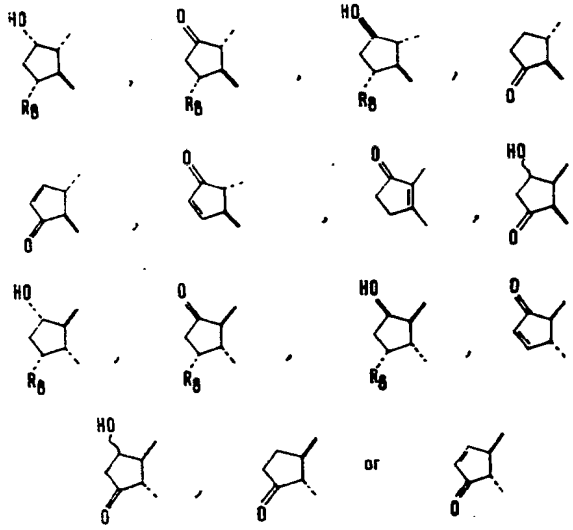
The present invention provides prostaglandin 1,15-lactones of the formula



wherein Z_1, Y_1, R_3, R_4, R_5 and R_7 are as defined above;

and

wherein ⑪ is



wherein R_8 is hydrogen or hydroxy; and

~ is as defined above or indicates attachment of the C—15 substituents in either alpha or beta configuration.

The lactones of this invention are useful for the same purposes, and by the same methods of administration, as the compounds of formula I. Accordingly, a pharmaceutical composition of the invention comprises a lactone of the invention in association with a pharmaceutically acceptable carrier. The advantages associated with the administration of prostaglandin lactones rather than the corresponding prostaglandins are described in our Application No. 26181/76 (Serial No. 1554023).

The following Charts show how known prostaglandins may be transformed to the 1,15-lactones of the invention. Preparations of some of the starting compounds are described in the appendix to our Application No. 26185/76 (Serial No. 1554025) and in our Applications Nos. 26212/76 (Serial No. 1554027) and 44458/77 (Serial No. 1554028).

CHART A

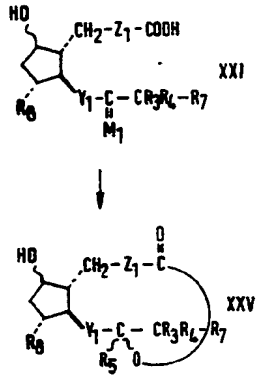


CHART B

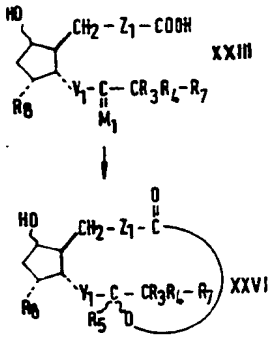


CHART C

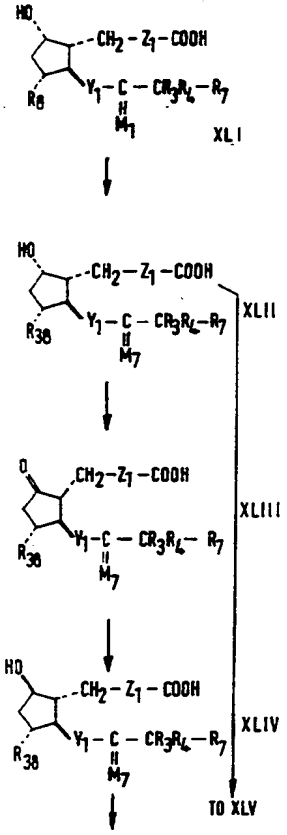
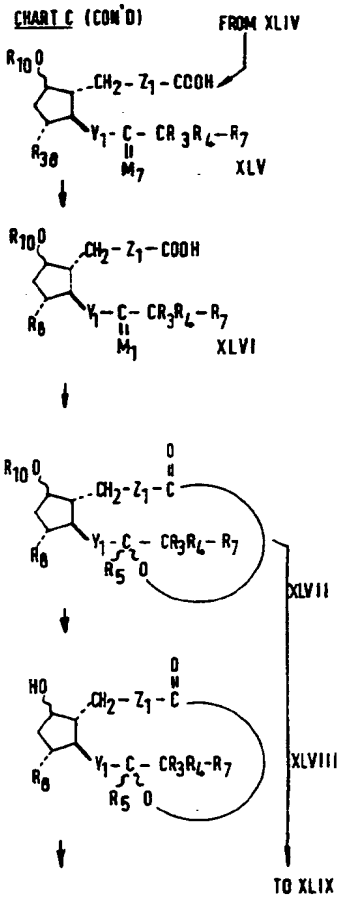


CHART C (CON'D)



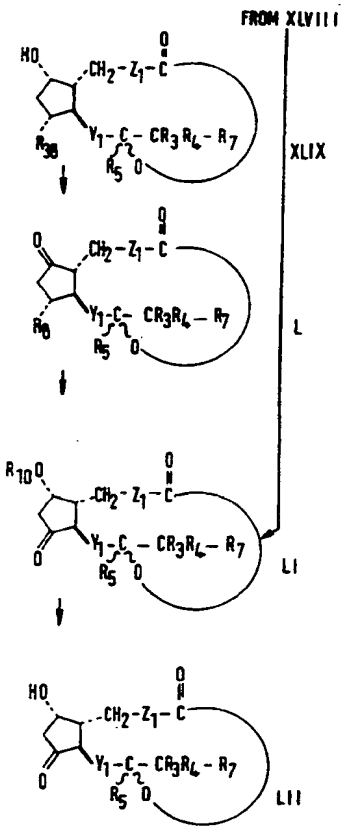
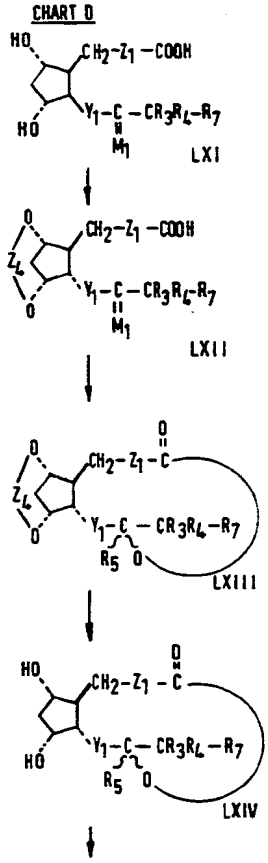


CHART D



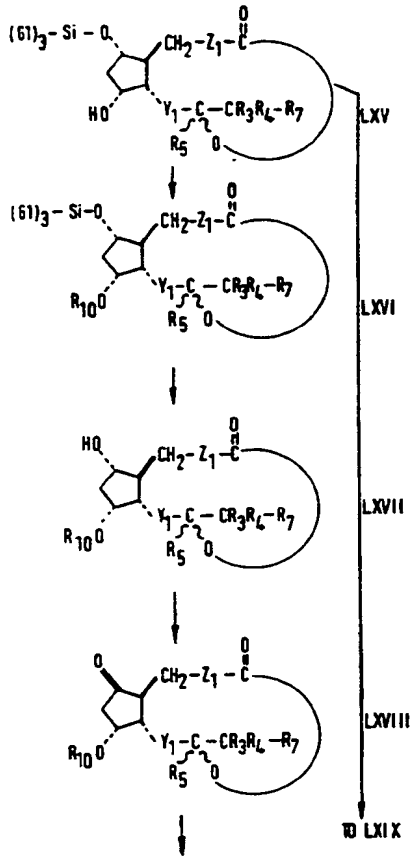

LXV
LXVI
LXVII
LXVIII
TO LXIX

CHART D (CON'D)

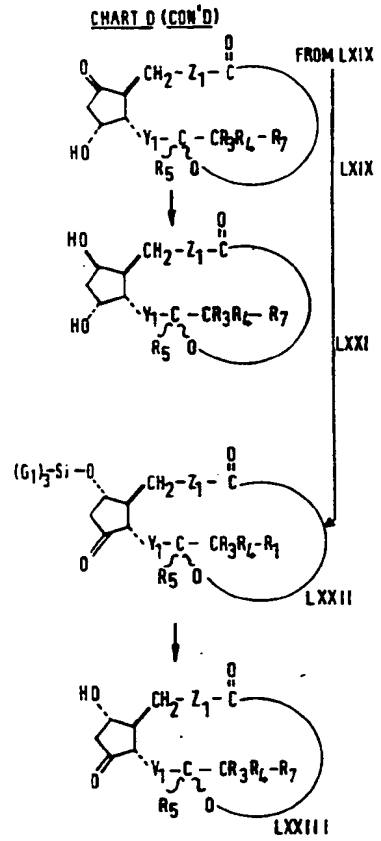
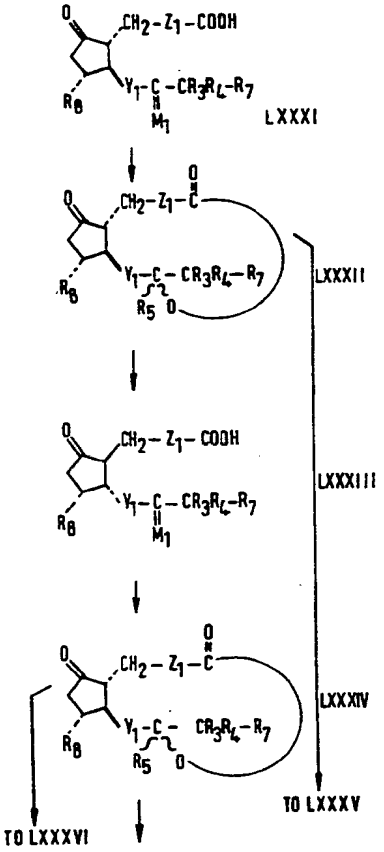

FROM LXIX
LXIX
LXXI
LXXII
LXXIII

CHART E



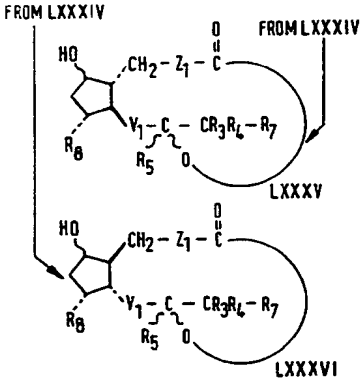
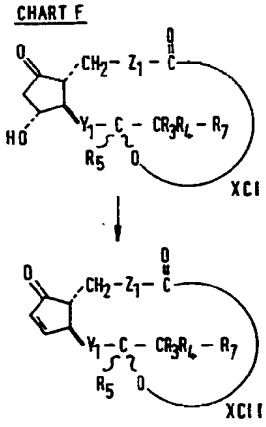


CHART F



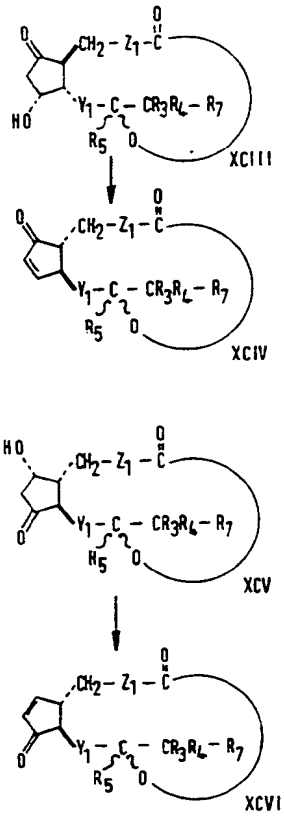


CHART F (CON'D)

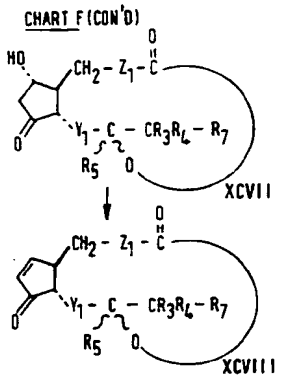
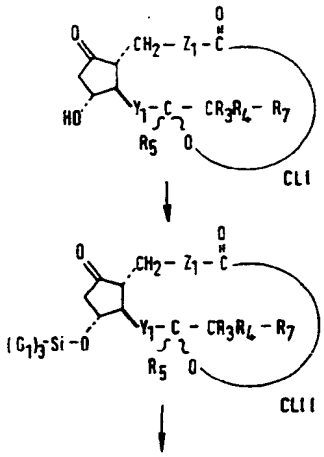
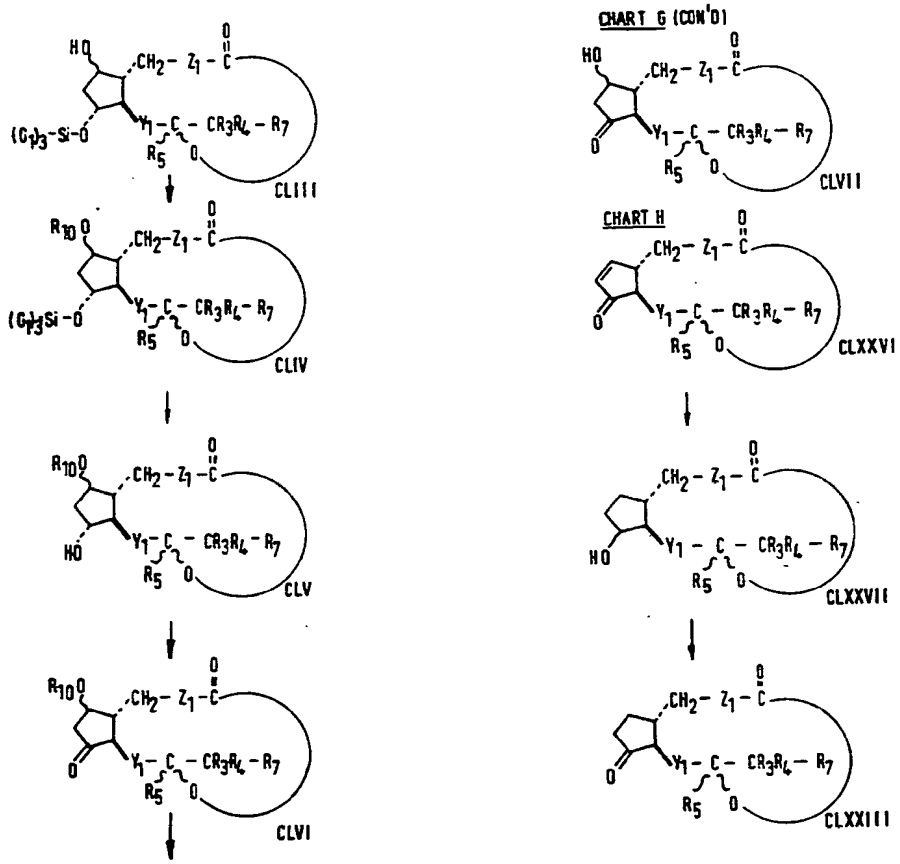


CHART G





South African Patent Specification No. 737,357 (Derwent Farmdoc CPI No. 28,414V) teaches the preparation of 1,9-lactones of certain PG-type compounds by application of heat to neat samples of the PG-type product. However, for the purposes of the present invention, the method described therein is unsuitable in that only complex mixtures of products are thereby produced.

A further method for lactonization of PG-type compounds is described by Japanese Patent Application No. 5—0037—793 (Derwent Farmdoc CPI No. 61147W) and Japanese Patent Application No. 5—0013—385 (Derwent Farmdoc CPI No. 56267W) wherein trifluoroacetic acid and trifluoroacetic anhydride are employed as lactonization agents. Further, lactonization for prostaglandin-type products is accomplished by the lactonization procedure of S. Masaume, Journal of the American Chemical Society 97, 3515 (1975). By this procedure a mercuric trifluoroacetate catalyzed ring closure of an ω hydroxy-t-butylthiol ester is employed.

However, the preferred procedure of lactonization of the prostaglandin analog described herein proceeds by transformation of the carboxyl of the prostaglandin type compound to a corresponding 2-pyridinethiol ester, followed by ring closure. The general method for this preferred lactonization process is described by E. J. Corey, Journal of the Americal Chemical Society 96, 5614 (1974), and its application to $PGF_{2\alpha}$ is described by E. J. Corey *et al.*, Journal of the American Chemical Society 97, 653 (1975). By this preferred procedure the formation of the 2-pyridinethiol ester proceeds by reaction of the prostaglandin type free acid with 1.5 equivalents of 2,2'-dipyridyl disulfide and 1.5 equivalents of triphenylphosphine in a dry (anhydrous) oxygen-free xylene or benzene. The 2-pyridinethiol esterification proceeds at room temperature, in 2—24 hr. The ring closure then proceeds by first diluting the thiol ester obtained above with dry, oxygen free xylene or benzene and thereafter heating to reflux for 1—24 hr.

A modification of the preferred procedure for lactonization is described by H. Gerlach *et al.*, Helv. Chim. Acta. 57 (8) 2661 (1974). This modification involves ring closure of an ω-hydroxy-2-pyridine thiol ester with silver ion (perchlorate or fluoroborate) catalysis in benzene at room temperature.

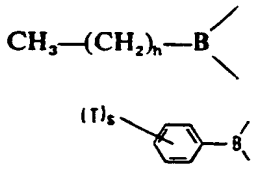
With respect to the above charts:

M_1, Y_1, Z_1, R_3, R_4, R_7 and R_8 are as defined above.

R_{10} is a blocking group.

R_{38} is —O—Si—$(G_1)_3$ wherein G_1 is alkyl, cycloalkyl, aralkyl, phenyl, or phenyl substituted with alkyl or halogen, the various G_1's of a —Si—$(G_1)_3$ radical being the same or different.

Z_4 is



wherein T and s are as defined above, and

wherein h is 2, 3 or 4, preferably 3.

M_7 is

wherein R_5 and G_1 are as defined above.

Those blocking groups within the scope of R_{10} are any group which replaces a hydroxy hydrogen and is neither attacked by nor as reactive to the reagents used in the transformations used herein as an hydroxy is and which is subsequently replaceable with hydrogen in the preparation of the prostaglandin-type compounds. Several blocking groups are known in the art, e.g. 2-tetrahydropyranyl and substituted 2-tetrahydropyranyl. See for reference E. J. Corey, Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research, 12, Organic Synthesis, pgs. 51—79 (1969). Those blocking groups which have been found useful include:

(a) 2-tetrahydropyranyl;

(b) 2-tetrahydrofuranyl; and

(c) a group of the formula

$$—C(OR_{11})(R_{12})—CH(R_{13})(R_{14}),$$

wherein R_{11} is alkyl of one to 18 carbon atoms, cycloalkyl of 3 to 10 carbon atoms, aralkyl of 7 to 12 carbon atoms, phenyl or phenyl substituted with one to 3 alkyl radicals of one to 4 carbon atoms; either R_{12} and R_{13} are the same or different and are each alkyl of one to 4 carbon atoms, phenyl or phenyl substituted with one, 2 or 3 alkyl radicals of one to 4 carbon atoms, or R_{12} and R_{13} are taken together and are $—(CH_2)_a—$ or $—(CH_2)_b—O—(CH_2)_c$, wherein a is 3, 4 or 5, or b is one, 2 or 3, and c is one, 2 or 3, with the proviso that b plus c is 2, 3 or 4; and R_{14} is hydrogen or phenyl.

When the blocking group R_{10} is 2-tetrahydropyranyl, the tetrahydropyranyl ether derivative of any hydroxy groups of the PG-type intermediates herein is obtained by reaction of the hydroxy-containing compound with 2,3-dihydropyran in an inert solvent, e.g. dichloromethane, in the presence of an acid condensing agent such as *p*-toluenesulfonic acid or pyridine hydrochloride. The dihydropyran is used in large stoichiometric excess, preferably 4 to 100 times the stoichiometric amount. The reaction is normally complete in less than an hour at 20 to 50°C.

When the blocking group is 2-tetrahydrofuranyl, 2,3-dihydrofuran is used, as described in the preceding paragraph, in place of the 2,3-dihydropyran.

When the blocking group is of the formula

$$—C(OR_{11})(R_{12})—CH(R_{13})(R_{14}),$$

wherein R_{11}, R_{12}, R_{13} and R_{14} are as defined above, the appropriate reagent is a vinyl ether, e.g. isobutyl vinyl ether or any vinyl ether of the formula

$C(OR_{11})(R_{12})=C(R_{13})(R_{14})$,

wherein R_{11}, R_{12}, R_{13}, and R_{14} are as defined above; or an unsaturated cyclic or heterocyclic compound, e.g. 1-cyclohexen-1-yl methyl ether, or 5,6-dihydro-4-methoxy-2*H*-pyran. See S. B. Reese *et al.*, Journal of the Chemical Society 89, 3366 (1967). The reaction conditions for such vinyl ethers and unsaturated compounds are similar to those for dihydropyran above.

The blocking groups according to R_{10} are removed by mild acidic hydrolysis. For example, by reaction with (1) hydrochloric acid in methanol; (2) a mixture of acetic acid, water, and tetrahydrofuran, or (3) aqueous citric acid or aqueous phosphoric acid in tetrahydrofuran, at temperatures below 55°C., hydrolysis of the blocking groups is achieved.

Various reactions in the succeeding charts introduce silyl groups of the formula $-Si(G_1)_3$. In some cases, such silylations are general, in that they silylate all hydroxy hydrogens, while in other cases they are selective, in that while one or more hydroxyls are silylated, at least one other hydroxyl remains unaffected. For any of these silylations, silyl groups within the scope of $-Si(G_1)3$ include trimethylsilyl, dimethylphenylsilyl, triphenylsilyl, t-butyldimethylsilyl, or methylphenylbenzylsilyl. With regard to G_1, examples of alkyl are methyl, ethyl, propyl, isobutyl, butyl, *sec-butyl*, *tert*-butyl and pentyl. Examples of aralkyl are benzyl, phenethyl, α-phenylethyl, 3-phenylpropyl, α-naphthylmethyl and 2-(β-naphthyl)-ethyl. Examples of phenyl substituted with halogen atoms or alkyl radicals are *p*-chlorophenyl, *m*-fluorophenyl, *o*-tolyl, 2,4-dichlorophenyl, *p-tert*-butylphenyl, 4-chloro-2-methylphenyl and 2,4-dichloro-3-methylphenyl.

These silyl groups are known in the art. See for example, Pierce "Silylation of Organic Compounds," Pierce Chemical Company, Rockford, Ill. (1968). When silylated products of the charts below are intended to be subjected to chromatographic purification, then the use of silyl groups known to be unstable to chromatography (e.g. trimethylsilyl) should be avoided. Further, when silyl groups are to be introduced selectively, silylating agents which are readily available and known to be useful in selective silylations are employed. For example, triphenylsilyl groups and t-butyldimethylsilyl groups are employed when selective introduction is required. Further, when silyl groups are to be selectively hydrolyzed over protecting groups according to R_{10}, then the use of silyl groups which are readily available and known to be easily hydrolyzable with tetra-n-butylammonium fluoride are employed. A particularly preferred group for this purpose is t-butyldimethylsilyl, although other silyl groups (e.g. trimethylsilyl) may also be used.

Chart A provides a method whereby the formula XXI PGF_α-, 11-deoxy-PGF_α-, PGF_β- or 11-deoxy-PGF_β-type compound is transformed to a formula XXV 1,15-lactone. Chart B provides a method whereby the corresponding 8β,12α-prostaglandin of formula XXIII is transformed to the corresponding formula XXVI 1,15-lactone. In both cases the lactonisation proceeds by the methods described above, to yield a mixture of the 1,9- and 1,15-lactones. The predominant product is the 1,9-lactone, as described and claimed in Application No. 26180/76 (Serial No. 1554024).

Chart C provides a method whereby the formula XLI PGF_α- or 11-deoxy-PGF_α-type compound is transformed to a formula XLVIII PGF_α-, 11-deoxy-PGF_α-PGF_β- or 11-deoxy-PGF_β-type 1,15-lactone, a formula L PGE- or 11-deoxy-PGE-type, 1,15-lactone or a formula LII PGD-type, 1,15-lactone.

By the procedure of Chart C the formula XLI compound is transformed to the formula XLII compound by selective silylation at C—11 and C—15 over C—9. Silyl groups according to the formula $-Si(G_1)_3$, wherein G_1 is defined above, are advantageously employed. For selective monosilylation procedures see U.S. Patent Specification No. 3,822,303, German Offenlegungsschrift No. 2,259,195 (Derwent Farmdoc CPI No. 36457U—B) or Netherlands Patent Specification No. 7,214,142 (Derwent Farmdoc CIP No. 26221U—B). Subsequently, there are performed the optional transformations of the formula XLII compound to the formula XLIII compound, and thereafter the formula XLIV compound. The formula XLIII compound is prepared from the formula XLII compound by oxidation of the 9-hydroxy to an oxo. Methods known in the art are employed. For example, the use of the Jones reagent or the Collins reagent or such additional reagents as are known to transform PGF_α-type compounds to corresponding PGE-type compounds is known and employed herein. Subsequently, the formula XLII compound is

transformed to the formula XLIV compound by reduction of the 9-oxo of the formula XLIII compound to the corresponding 9-hydroxy compound and separation of the 9β-hydroxy isomer from the isomeric mixture so formed. This reduction is performed by methods known in the art. For example, the use of sodium, potassium or lithium borohydride reducing agents and such other agents as is known in the art for reduction of PGE-type compounds to mixtures of PGF_α and PGF_β-type compounds is known and employed herein. The 9-epimeric mixture is conveniently separated by silica gel chromatography, yielding the formula XLIV product.

Thereafter, the formula XLII or formula XLIV compounds are transformed to the formula XLV compound by replacing the 9-hydroxy hydrogen with a blocking group according to R_{10}. Methods known in the art and hereinabove described are employed. Thereafter the formula XLV compound is transformed to the formula XLVI compound by selective hydrolysis of any silyl groups over any blocking groups according to R_{10}. This selective removal of any silyl groups is accomplished by methods known in the art. See for reference Corey *et al.*, Journal of the American Chemical Society 94, 6190 (1972). An especially useful reagent for this purpose is tetra-n-butylammonium fluoride in tetrahydrofuran.

Thereafter the formula XLVI compound is transformed to the formula XLVII compound by 1,15-lactonization. Lactonization methods described above are employed.

The formula XLVIII PGF_α-, 11-deoxy-PGF_α-, PGF_β-, or 11-deoxy-PGF_β-type, 1,15-lactones are then prepared from the formula XLVII compound by hydrolysis of the blocking group according to R_{10}. This hydrolysis proceeds by methods hereinabove described.

The formula L PGE- or 11-deoxy-PGE-type, 1,15-lactone is then prepared from the formula XLVIII PGF_α- or 11-deoxy-PGF_α-type, 1,15-lactone by first selective silylation at C—11 over C—9 (formula XLIX) employing methods described in the transformation of the formula XLI compound to the formula XLII compound; oxidizing the formula XLIX silylated compounds so formed to a corresponding 9-oxo compound, employing methods known in the art for transformation of PGF_α-type compounds to PGE-type compounds as described above; and thereafter optionally hydrolyzing any silyl group employing methods and procedures known in the art.

Alternatively the formula XLVII compound is employed in the preparation of the formula LI compound. In this transformation the 11-hydroxy of the formula XLVII compound is oxidized to the corresponding formula LI 11-oxo compound. Procedures known in the art are employed. For example, see Tetrahedron Letters, 2235 (1974). Useful reagents for this purpose include those oxidizing reagents described above as useful in the transformation of PGF-type compounds to PGE-type compounds. The formula LI compound is then hydrolyzed at C—9, preparing the formula LII PGD-type, 1,15-lactone.

Chart D provides a method whereby the formula LXI 8β,12α-PGF_α-type compound is transformed to a formula LXIV 8β,12α-PGF_α-type, 1,15-lactone; a formula LXIX 8β,12α-PGE-type, 1,15-lactone; a formula LXXI 8β,12α-PGF_β-type, 1,15-lactone; or a formula LXXIII 8β,12α-PGD-type, 1,15-lactone. Additionally, the transformations of the formula LXI compound to the formula LXII compound are optionally employed on the 8,12-isomers of those depicted by formulas LXI to LXIV, respectively, thereby preparing the PGF_α-type, 1,15-lactone corresponding to formula LXIV.

The formula LXII compound is prepared from the formula LXI compound by cyclo(alkyl or arylboronisation). Accordingly, the bicyclic formula LXII compound is prepared by reaction of the formula LXI compound with a slight stoichiometric excess of a corresponding alkyl or arylboronic acid. The course of the reaction is conveniently monitored by gas chromatography and the reaction is preferably carried out with vigorous stirring at reflux. The preferred reaction diluent for this transformation is methylene chloride, although, alternatively, other suitable organic solvents may be employed. The formula LXII compound is then lactonised by one of the methods described above to form the formula LXXII compound. The product is decyclo(alkylboronised) using an alkali metal hydroxide, e.g. sodium, lithium or potassium hydroxide, in a water-miscible diluent capable of yielding a homogeneous reaction mixture, e.g. methanol or ethanol. The resulting solution is then treated with dilute aqueous hydrogen peroxide. Accordingly, the 8β,12α-PGF_α-type, 1,15-lactones are prepared.

Thereafter, the formula LXIV compound is transformed to the formula LXV

compound by selective silylation of the C—9 hydroxy over the C—11 hydroxy, as described above for the XLI to XLII transformation. Thereafter, the formula LXV compound is employed in the preparation of either the formula LXVI compound or the formula LXXII compound.

The formula LXV compound is transformed to the formula LXVI compound by replacing the 11-hydroxy hydrogen with a blocking group according to R_{10}. Methods known in the art, as described above, are employed.

The formula LXVI compound is then transformed to the formula LXVII compound by selective hydrolysis of the silyl group over the blocking group according to R_{10}. Methods hereinabove described for such selective hydrolysis are employed. See the transformation of the formula XLIV compound to the formula XLVI compound of Chart C.

Thereafter, the formula LXVII compound is transformed to the formula LXVIII compound by oxidation of the 9-hydroxy to a corresponding 9-oxo compound. Reagents and procedures known in the art for transformation of PGF_α-type compounds to PGE-type compounds are employed. The formula LXVIII compound is then hydrolyzed, whereby blocking groups according to R_{10} are removed, thereby preparing the formula LXIX 8β,12α-PGE-type, 1,15-lactone. Methods of hydrolysis of blocking groups according to R_{10} hereinabove described are employed.

Thereafter the formula LXIX compound is transformed to the formula LXXI compound by a ring carbonyl reduction, employing methods known in the art for the transformation of PGE-type compounds to the corresponding PGF_β compounds. Accordingly, sodium, potassium or lithium borohydride is employed in the reduction, followed by chromatographic separation of the 9β-hydroxy epimer from the 9-epimeric mixture so formed. Accordingly, there are prepared 8β,12α-PGF_β-type, 1,15-lactones of formula LXXI.

The formula LXV compound is employed in the preparation of the formula LXXII compound by selective oxidation of the C—11 hydroxy to a corresponding oxo. Methods described above for the transformation of formula LXVII compounds to formula LI compounds are employed. Thereafter the formula LXXII compound is transformed to the formula LXXIII 8β,12α-PGD-type, 1,15-lactone following procedures described above for hydrolysis of silyl groups.

Chart E provides a method whereby the formula LXXXI PGE- or 11-deoxy-PGE-type starting material is transformed to the formula LXXXII PGE- or 11-deoxy-PGE-type, 1,15-lactones, or the formula LXXXV PGF_α-, 11-deoxy-PGF_α-, PGF_β-, or 11-deoxy-PGF_β-type, 1,15-lactones. Further, Chart E describes the use of the formula LXXXIII 8β,12α-PGE- or 11-deoxy-8β,12α-PGE-type compound in the preparation of the formula LXXXIV 8β,12α-PGE- or 11-deoxy-8β,12α-PGE-type, 1,15-lactones or the formula LXXXVI 8β,12α-PGF_α-, 11-deoxy-8β,12α-PGF_α-, 8β,12α-PGF_β-, or 11-deoxy-8β,12α-PGF_β-type, 1,15-lactones.

For the transformation of the formula LXXXI or LXXXIII compound to the formula LXXXII or formula LXXXIV compound, respectively, lactonization methods described above are employed. Thereafter, the formula LXXXIV or formula LXXXVI compound is prepared from the formula LXXXIII compound, respectively, by a ring carbonyl reduction, followed by separation of C—15 epimers. These ring carbonyl reductions and epimeric separations are performed by methods described hereinabove. See the transformation of the formula XLIII compound to the formula LXIV compound of Chart C.

Chart F provides a method whereby the formula XCI PGE-type compound is transformed to the formula XCII PGA-type, 1,15-lactone; the formula XCIII 8β,12α-PGE-type, 1,15-lactone is transformed to the formula XCIV 8β,12α-PGA-type, 1,15-lactone; a formula XCV PGD-type, 1,15-lactone is transformed to a formula XCVI 9-deoxy-9,10-didehydro-PGD-type, 1,15-lactone; or a formula XCVII 8β,12α-PGD-type, 1,15-lactone is transformed to a formula XCVIII 9-deoxy-9,10-didehydro-8β,12α-PGD-type, 1,15-lactone.

For each of the above transformations of Chart F, the hydroxyl on the cyclopentane ring is dehydrated to the corresponding compound with α,β-unsaturation to the ketone employing mild acidic dehydration. For example, methods known in the art for the transformation of PGE-type compounds to PGA-type compounds are employed. Alternatively, the various starting materials of Chart F are transformed to the corresponding acetates using, for example, acetic anhydride, and are then chromatographed on silica gel to effect the desired dehydration.

PGA-, PGB- and 11-deoxy-PGE-type compounds corresponding to formula I, and their respective 8β,12α-isomers, contain only one hydroxy group, at the C—15 position. These compounds can therefore be directly transformed to the corresponding 1,15-lactones without the need for any selective blocking procedures. The lactonisation methods which are used are those described above.

Chart G provides a method whereby the formula CLI PGE-type 1,15-lactone or its 8β,12α-isomer is transformed to a corresponding formula CLVII 9β-PGD- or PGD-type 1,15-lactone, or its 8β,12α-isomer, respectively.

With respect to Chart G, the formula CXLII compound is prepared from the formula CXLI compound by known silylation methods, as described above. The formula CXLIII compound is then prepared from the formula CXLII compound by a ring carbonyl reduction, employing methods described above. The 9-epimeric mixture which is prepared is then separated by silica gel chromatography, preparing the separated formula CLIII epimers.

The formula CLIV compound is then prepared from the formula CLIII compound by transforming the 9-hydroxy hydrogen to a R_{10} blocking group by the methods described above.

Thereafter the silyl groups are selectively hydrolysed over the blocking groups according to R_{10}, following the procedure described above for Chart C for the transformation of the formula XLV compound to the formula XLVI compound. Thereupon, the formula CXLV compound is oxidised at the C—11 position to the corresponding 11-oxo compound, using methods described above.

The reaction sequence of Chart H proceeds by methods known in the art for transforming PGA-type compounds to corresponding 11-deoxy-PGE-type compounds. Accordingly, the formula CLXXVI starting material is subjected to a potassium, sodium or lithium borohydride reduction, as is known in the art. The reaction is usually carried out at about −20°C., and is ordinarily complete within a few minutes. The formula CLXXVII compound which is thus obtained is then oxidised to the formula CLXXVIII 9-deoxy-PGD-type 1,15-lactone employing oxidation agents known in the art for this purpose, e.g. the Jones or Collins reagent as described above, are employed.

The introduction of silyl groups or R_{10} blocking groups in place of the hydroxy hydrogen at C—15 is not required for the various transformations of the above Charts when the 15-methyl compounds are employed. Accordingly, when the 15-hydroxy hydrogen is the only hydroxy hydrogen to be blocked or silylated, then such blocking or silylation may be omitted. Further, when one or both of any secondary hydroxyls at C—9 or C—11 are to be blocked or silylated in addition to the C—15 tertiary hydroxyl, then the transformation effecting the blocking or silylation need only be carried out until any secondary hydroxyls have been so transformed.

However, when the hydroxy hydrogen of a 15-methyl-PG-type compound is replaced with a R_{10} blocking group then the subsequent hydrolysis of the blocking group in many cases epimerises the C—15 hydroxyl. In such cases, epimeric purity of the product then requires separation employing silica gel chromatography or high pressure liquid chromatography, or other techniques known to separate prostaglandin-type diastereoisomers.

The following Preparations and Examples illustrate how the compounds of this invention may be prepared.

IR (infrared) absorption spectra are recorded on a Perkin-Elmer Model 421 infrared spectrophotometer. Except when specified otherwise, undiluted (neat) samples are used.

NMR (Nuclear Magnetic Resonance) spectra are recorded on a Varian A—60, A—60D, and T—60 spectrophotometer on deuterochloroform solutions with tetramethylsilane as an internal standard (downfield). "Varian" is a registered Trade Mark.

Mass spectra are recorded on an CEC model 21—110B Double Focusing High Resolution Mass Spectrometer on an LKB Model 9000 Gas-Chromatograph-Mass Spectrometer. Trimethylsilyl derivatives are used, except where otherwise indicated.

The collection of chromatographic eluate fractions starts when the eluant front reaches the bottom of the column.

"Brine", herein, refers to an aqueous saturated sodium chloride solution.

The A—IX solvent system used in thin layer chromatography is made up from ethyl acetate-acetic acid-cyclo-hexane-water (90:20:50:100 v/v/v/v) as modified from M. Hamberg and B. Samuelsson, J. Biol. Chem. 241, 257 (1966).

Skellysolve B (SSB) refers to mixed isomeric hexanes.

Silica gel chromatography, as used herein, is understood to include elution, collection of fractions, and combination of those fractions shown by TLC (thin layer chromatography) to contain the pure product (i.e. free of starting material and impurities).

Melting points (MP) are determined on a Fisher-Johns or Thomas-Hoover melting point apparatus.

THF refers to tetrahydrofuran.

Preparation 1.

$PGF_{2\alpha}$ 1,15-lactone

Refer to Chart A.

A. A solution of 35 mg. of $PGF_{2\alpha}$, 39 mg. of triphenylphosphine and 33 mg. of 2,2'-dipyridyl disulfide in 0.5 ml. of dry, oxygen-free benzene is stirred at 25°C. for 18 hr. The resulting mixture is then diluted with 25 ml. of benzene and heated at reflux for 24 hr. Thin layer chromatographic analysis in 15% by volume acetone and methylene chloride indicates a mixture of $PGF_{2\alpha}$ 1,9-lactone and 1,15-lactone in a ratio of about 8:1. Pure product is then isolated from the reaction mixture employing silica gel chromatographic separation.

Preparation 2.

$PGF_{2\alpha}$ 1,15-lactone

Refer to Chart D.

A. A solution of 5.5 g. of $PGF_{2\alpha}$ and 1.79 g. of n-butylboronic acid in 150 ml. of methylene chloride is heated at reflux for 15 min. Thereafter about half the methylene chloride is removed by distillation at atmospheric pressure and additional methylene chloride added to restore the volume to 150 ml. This distillation and replacement of methylene chloride is then repeated 3 times, after which all solvent is then removed under reduced pressure. Thereupon, crude formula LXII compound is obtained.

B. The reaction product of part A is then dissolved in 180 ml. of anhydrous oxygen-free xylene and treated with 5.128 g. of 2,2'-dipyridyl disulfide, followed by addition of 6.27 g. of triphenylphosphine. After 18 hr. at 25°C. under a nitrogen atmosphere the above solution is diluted with 300 ml. of oxygen free xylene and thereafter added dropwise over a 10 hr. period to 3.2 l. of vigorously stirred refluxing xylene under a nitrogen atmosphere. After the addition is complete, 100 ml. of xylene is distilled off and the solution is heated at reflux for 24 hr. The reaction mixture is then cooled and the xylene removed under reduced pressure, preparing a formula LXIII compound.

C. The reaction product of part B is then taken up in 500 ml. of tetrahydrofuran and treated with 10 ml. of 30 percent hydrogen peroxide and 100 ml. of saturated aqueous sodium bicarbonate. This mixture is then stirred vigorously for 30 min. at 35°C. and then concentrated under reduced pressure. The residue is then taken up in brine and ethyl acetate and extracted thoroughly with ethyl acetate. The combined organic layer is then washed with 1N aqueous potassium bisulfate, water, aqueous sodium bicarbonate, and brine. After drying over sodium sulfate, removal of the solvent affords a viscous yellow oil which is chromatographed on 500 g. of acid washed silica gel. The column is packed with 25 percent by volume ethyl acetate and hexane and eluted with 50 percent by volume ethyl acetate and hexane. Title product is then crystallized from 40 ml. of diethylether and hexane (1:1 v/v), affording 1.559 g. of title product. Melting point is 110—111°C. Infrared absorptions are observed at 3500, 3370, 3290, 3010, 1700, 1320, 1310, 1290, 1260, 1105, 1080, 1055, 970, and 730 $cm.^{-1}$. NMR absorptions are observed 6.00—5.75, 5.75—4.95, 4.30—3.85, and 2.65 δ. The mass spectrum shows parent peak 480.3102 and other peaks at 465, 436, 409, 390, 380, 364, 238, and 217.

Following the procedure of Preparation 2, but employing each of the various PGF_{α}-type compounds described by formula 1 in place of $PGF_{2\alpha}$, there are obtained each of the various corresponding PGF_{α}-type, 1,15-lactones.

Example 1.

$8\beta,12\alpha$-$PGF_{2\alpha}$, 1,15-lactone

Refer to Chart D.

Following the procedure of Preparation 2, but employing $8\beta,12\alpha$-$PGF_{2\alpha}$ in

place of $PGF_{2\alpha}$, there is obtained the title product.

Following the procedure of Example 1, but employing each of the various $8\beta,12\alpha$-PGF_α-type compounds described by formula 1 in place of $8\beta,12\alpha$-$PGF_{2\alpha}$, there are obtained each of the various corresponding $8\beta,12\alpha$-PGF_α-type, 1,15-lactones.

Example 2.
PGE_2, 1,15-lactone

Refer to Chart C.

A. A solution of 1.7 g. of $PGF_{2\alpha}$, 1,15-lactone (formula XLVIII) in 45 ml. of anhydrous acetone is cooled under nitrogen to between −45 and −40°C. This solution is then treated with 4.5 ml. of trimethylsilyldiethylamine. After addition is complete, the mixture is stirred at −45 to −40°C. for 2 hr. This mixture is then cooled to −78°C., diluted with 150 ml. of precooled diethyl ether, and poured into an ice-brine mixture. After extraction with hexane, the combined organic layers are washed with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Thereby, 1.47 g. of a formula XLIX 11-trimethylsilyl compound is obtained.

B. The Collins reagent is prepared by adding 2.45 g. of dry chromium trioxide to a cold (0° C.), stirred solution of 3.99 ml. of anhydrous pyridine in 120 ml. of methylene chloride. The resulting dark resolution is then stirred at 25°C. for one hr., then cooled to 0°C. A solution of the reaction product of part A in 6 ml. of methylene chloride is then added in one portion to the rapidly stirred Collins reagent. The ice bath is then removed and the reaction mixture is stirred an additional 20 min. The mixture is then poured into a column containing 150 g. of neutral silica gel. The column is then eluted with ethyl acetate yielding 1.357 g. of PGE_2, 1,15-lactone, 11-trimethylsilyl ether.

The reaction product of part B is then dissolved in 150 ml. of methanol, diluted with 60 ml. of aqueous 2.5 percent w/v citric acid, and stirred at 25°C. for 30 min. After removal of about half of the methanol by evaporation at reduced pressure, the remaining solution is diluted with brine and extracted with ethyl acetate. The combined organic extracts are then washed with aqueous sodium bicarbonate and brine, dried over sodium sulfate, and concentrated.

The crude product is then crystallized from diethyl ether and hexane, yielding 6.08 g. of title product.

Following the procedure of Example 2, but employing each of the various PGF_α-type, 1,15-lactones described following Preparation 2, in place of $PGF_{2\alpha}$, 1,15-lactone, there are obtained each of the various corresponding PGE-type, 1,15-lactones.

Alternatively, the title compound of Example 2 or each of the various compounds described in the paragraph are obtained directly by lactonization of PGE_2 or a PGE-type compound by the procedure described in Preparation 1.

Example 3.
$8\beta,12\alpha$-PGE_2, 1,15-lactone

A. The method of Chart D:

(1) Following the procedure of Example 11 of Application No. 26180/76, (Serial No. 1554024), $8\beta,12\alpha$-$PGF_{2\alpha}$, 1,15-lactone (Preparation 2) is selectively silylated at C—9.

(2) Following the procedure part A of Example 8 of Application No. 26180/76, (Serial No. 1554024), the reaction product of part (1) above is transformed to the corresponding 11-(tetrahydropyranyl ether), a formula LXVI compound.

(3) Following the procedure of part 6 of Example 1 of Application No. 26185/76 (Serial No. 1554025), the reaction product of part (2) above is selectively hydrolyzed at C—9 (the silyl ether), preparing $PGF_{2\alpha}$, 1,15-lactone, 11-(tetrahydropyranyl ether), a formula LXVII compound.

(4) Following the procedure of part C of Example 8 of Application No. 26180/76 (Serial No. 1554024), the reaction product of part (3) above is transformed to the corresponding PGE_2-type, 1,11-lactone (formula LXVIII).

(5) Following the procedure of part D of Example 8 of Application No. 26180/76 (Serial No. 1554024), the reaction product of subpart 4 above is hydrolyzed to the title product.

B. Alternatively, the title product is prepared by lactonization of $8\beta,12\alpha$-PGE_2, following the procedure of Preparation 1.

Following the procedure of Example 3, but employing each of the various

8β,12α-PGF_α-type 1,15-lactones described following Example 1 or each of the various 8β,12α-PGE-type compounds described by formula XLI, respectively, in place of 8β,12α-$PGF_{2\alpha}$, 1,15-lactone or 8β,12α-PGE_2, respectively, there are obtained each of the various 8β,12α-PGE-type, 1,15-lactones.

Example 4.

$PGF_{2\beta}$, 1,15-lactone

Refer to Chart D or E.

Following the procedure of part A(2) of Example 12 of Application No. 26180/76 (Serial No. 1554024), the reaction product of Example 2 is reduced and chromatographed to yield the title product.

Following the procedure of Example 4, but employing each of the various PGE-type 1,15-lactones described following Example 2, in place of PGE_2, 1,15-lactone, there are obtained each of the various corresponding PGF_β-type, 1,15-lactones.

Example 5.

8β,12α-$PGF_{2\beta}$, 1,15-lactone

Refer to Chart E.

Following the procedure described in part A(2) of Example 12 of Application No. 26180/76 (Serial No. 1554024), 8β,12α-PGE_2, 1,15-lactone is reduced and chromatographed to yield the title product.

Following the procedure of Example 5, but employing each of the various 8β,12α-PGE-type, 1,15-lactone described following Example 3 in place of 8β,12α-PGE_2, 1,15-lactone, there are obtained each of the various corresponding 8β,12α-PGF_β-type, 1,15-lactones.

Example 6.

11-Deoxy-PGE_2, 1,15-lactone

Following the procedure of Preparation 1, 11-deoxy-PGE_2 is lactonized to form the title product.

Following the procedure of Example 6, but employing each of the various 11-deoxy-PGE-type compounds described by formula I in place of 11-deoxy-PGE_2, there are obtained each of the various corresponding 11-deoxy-PGE-type, 1,15-lactones.

Example 7.

11-Deoxy-8β,12α-PGE_2

Following the procedure of Preparation 1, 11-deoxy-8β,12α-PGE_2 is lactonized to the title product.

Following the procedure of Example 7, but employing each of the various 11-deoxy-8β, 12α-PGE-type compounds described by formula I in place of 11-deoxy-8β,12α-PGE_2, there are obtained each of the various corresponding 8β,12α-11-deoxy-PGE-type, 1,15-lactones.

Example 8.

11-Deoxy-$PGF_{2\alpha}$ 1,15-lactone or 11-deoxy-$PGF_{2\beta}$ 1,15-lactone

Refer to Chart E.

Following the procedure of part A(2) of Example 12 of Application No. 26180/76 (Serial No. 1554024), 11-deoxy-PGE_2, 1,15-lactone is reduced and chromatographed yielding the title products.

Following the procedure of Example 8, but employing each of the various 11-deoxy-PGE-type, 1,15-lactones described following Example 6 in place of 11-deoxy-PGE_2, 1,15-lactone, there are obtained each of the various corresponding 11-deoxy-PGE-type, 1,15-lactones.

Example 9.

11-deoxy-8β,12α-$PGF_{2\alpha}$ 1,15-lactone or 11-deoxy-8β,12α-$PGF_{2\beta}$ 1,15-lactone

Refer to Chart E.

Following the procedure of part A(2) of Example 12 of Application No. 26180/76 (Serial No. 1554024), 11-deoxy-8β,12α-PGE_2 1,15-lactone is reduced and chromatographed yielding the title products.

Following the procedure of Example 9, but employing each of the various 8β,12α-PGE-type, 1,15-lactones described following Example 7, in place of 8β,12α-

PGE_2, 1,15-lactone there are obtained each of the various corresponding PGE-type, 1,15-lactones.

Example 10.
PGA_2, 1,15-lactone

A. The method of Chart F:

(1) PGE_2, 1,15-lactone is dissolved in pyridine, combined with one equivalent of acetic anhydride and allowed to stand at 25°C. for 3 hr. Thereupon, PGE_2, 1,15-lactone, 11-acetate is prepared. The reaction mixture is then cooled in an ice bath treated dropwise over 15 min. with 20 ml. of methanol. The ice bath is then allowed to melt and the temperature allowed to rise to ambient temperature. After an additional 18 hr., the reaction mixture is then poured into a mixture of ice, diethyl ether, water, and 70 ml. of 2N aqueous potassium bisulfate. This mixture is then extracted thoroughly with diethyl ether and ethereal extract washed with water, aqueous sodium bicarbonate and brine. This mixture is then dried over anhydrous sodium sulfate and concentrated under reduced pressure.

(2) The crude product of part (1) above is then chromatographed on 100 g. of neutral silica gel. The column is packed and diluted with 15 percent by volume ethyl acetate and hexane. Thereupon 46 mg. of title product are obtained. This material crystallizes on standing and recrystallization is effected from diethyl ether and hexane. The melting point is 60—61.5°C. NMR absorptions are observed at 7.50—7.33 and 6.27 to 6.06. The mass spectrum shows parent peak 316.2074 and other peaks 298, 288, 259, 229, and 198. Infrared absorptions are observed at 3010, 1715, 1705, 1580, 1355, 1345, 1325, 1245, 1170, 1145, 1140, 1035, and 970 $cm.^{-1}$.

B. Alternatively, the title product is prepared from PGA_2 by direct lactonization according to Preparation 1.

Following the procedure of Example 10, but employing each of the various PGE-type, 1,15-lactones described following Example 6 or PGA-type compounds described by formula LXI, respectively, there are obtained each of the various corresponding PGA-type, 1,15-lactones.

Example 11.
$8\beta,12\alpha$-PGA_2, 1,15-lactone

Following the procedure of part A or part B of Example 10, $8\beta.12\alpha$-PGE_2, 1,15-lactone or $8\beta,12\alpha$-PGA_2, respectively, is transformed to the title product.

Following the procedure of Example 11, but employing each of the various $8\beta,12\alpha$-PGE-type, 1,15-lactones described following Example 7 or PGA-type compounds described by formula I, in place of $8\beta,12\alpha$-PGE_2, 1,15-lactone or $8\beta,12\alpha$-PGA_2, respectively, there are obtained each of the various corresponding $8\beta,12\alpha$-PGA-type, 1,15-lactones.

Example 12.
PGB_2, 1,15-lactone

PGB_2 (0.334 g.), 5 ml. of dry, oxygen-free xylene, 0.393 g. of triphenylphosphine, and 0.33 g. of 2,2'-dipyrididyl sulfide are stirred at room temperature under a nitrogen atmosphere for 6 hr. The resulting mixture is then diluted with 250 ml. of dry, oxygen-free xylene, and the solution heated at reflux for 16 hr. The resulting mixture is then concentrated under reduced pressure at a bath temperature of 40°C. to remove the xylene. The residue is then chromatographed on a dry pack column of 100 g. of silica gel and 20 ml. of diethyl ether. The column is then eluted with 60 percent by volume diethyl ether and hexane. Thereupon 200 mg. of PGB_2, 1,15-lactone are obtained. Silica gel R_f is 0.37 in diethyl ether and hexane (1:1 v/v). The mass spectrum shows parent peak 316.2021 and other peaks at 298, 288, 269, and 217. Characteristic NMR absorptions are observed at 5.97—6.80, 5.07—5.70, and 2.83—3.12 δ. UV absorption is observed at 277 $m\mu$ (ε = 16,800).

Following the procedure of Example 12, but employing each of the various PGB-type compounds described by formula I in place of PGB_2, there are obtained each of the various corresponding PGB-type, 1,15-lactones.

Example 13.
PGD_2, 1,15-lactone.

Refer to Chart C.

A. Method employing $PGF_{2\alpha}$, 1,15-lactone as starting material:

(1) To a stirred solution at 0°C. of 1.0 g. of $PGF_{2\alpha}$, 1,15-lactone and 3 ml. of

anhydrous dimethylformamide is added at 0°C. a solution of 474 mg. of t-butyldimethylsilyl chloride and 428 mg. of imidazole in 3 ml. of dimethylformamide. The resulting mixture is then stirred for one hr. at 0°C. under nitrogen, then poured into brine, and extracted with hexane. The combined organic layer is then washed successively with water, cold aqueous sodium bisulfate, water, aqueous sodium bicarbonate, and brine. The organic layer is then dried over sodium sulfate and concentrated under reduced pressure. The crude product is then chromatographed on 140 g. of neutral silica gel. The column is packed with 5 percent by volume ethyl acetate and hexane and diluted with 20 percent by volume ethyl acetate and hexane. Thereupon, 1.10 g. of $PGF_{2\alpha}$, 1,15-lactone, 11-(t-butyldimethylsilyl ether) are obtained. Infrared absorptions are observed at 3500, 1730, 1460, 1240, 1125, 1110, 1040, 1005, 975, 880, 854, 840, and 780 $cm.^{-1}$. NMR absorptions are observed at 5.90—4.95, 4.25—3.75, 3.70, and 0.85 δ.

(2) A solution of 1.05 g. of the reaction product of part (1) above, 5 ml. of freshly distilled dihydropyran, and 50 mg. of pyridine hydrochloride in 25 ml. of anhydrous methylene chloride are stirred under a nitrogen atmosphere at 25°C. for 18 hr. The reaction mixture is then poured into a mixture of ice, sodium bicarbonate, and water, and extracted thoroughly with hexane. The organic extracts are then washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to yield a crude product (1.4 g.) which is chromatographed on 140 g. of neutral silica gel. The column is packed with 5 percent by volume ethyl acetate and hexane and diluted with 10 percent by volume ethyl acetate in hexane. Thereupon 1.16 g. of $PGF_{2\alpha}$, 1,15-lactone, 9-(tetrahydropyranyl ether), 11-(t-butyldimethylsilyl ether) are obtained. Infrared absorptions are observed at 1740, 1460, 1350, 1240, 1140, 1120, 1040, 1020, 990, 975, 860, 840, and 780 $cm.^{-1}$. Infrared absorptions are observed at 5.95—5.0, 4.75—4.50, 4.30—3.25, and 0.88 δ.

(3) To a solution of 1.17 g. of the reaction product of subpart (2) above in 5 ml. anhydrous tetrahydrofuran at 25°C. is added under a nitrogen atmosphere 22 ml. of a 0.3M solution of tetra-n-butyl ammonium fluoride in tetrahydrofuran. The reaction mixture is then stirred for 30 min. at 25°C., then poured into a mixture of ice, water, sodium bicarbonate, and hexane. The resulting mixture is then extracted thoroughly with hexane and the organic extracts are then washed with brine, dried over sodium sulfate, and evaporated. The crude product (1.1 g.) is used without further purification. A 75 mg. sample of this crude product, however, is chromatographed on 15 g. of neutral silica gel, packed with 10 percent by volume ethyl acetate in hexane and eluted with 10 percent by volume ethyl acetate in hexane. Accordingly, 16 mg. of pure $PGF_{2\alpha}$, 1,15-lactone, 9-(tetrahydropyranyl ether) are obtained. Infrared absorptions are observed 3500, 1730, 1440, 1340, 1240, 1200, 1160, 1140, 1120, 1080, 1040, 1020, 990, 970, 920, 870, 815, and 735 $cm.^{-1}$. NMR absorptions are observed at 6.0—5.0, 5.75—5.0, 4.35—3.30, and 2.35 δ.

(4) A solution of 920 mg. of the reaction product of subpart (3) above in 30 ml. of acetone is cooled to between −20 and −30°C. This cooled mixture is then treated dropwise with 0.8 ml. of the Jones reagent. After 75 min. at −20 to −30°C., 0.5 ml. of isopropyl alcohol is added to destroy excess oxidizing reagent. After an additional 10 min. of stirring at −25°C., the mixture is diluted with 400 ml. of water and extracted thoroughly with a mixture of hexane and ethyl acetate (4:1 v/v). The combined organic extracts are then washed successively with water, ice cold aqueous sodium bisulfate, water, aqueous sodium bicarbonate, and brine. The organic extract is then dried over sodium sulfate and concentrated under reduced pressure. This crude (900 mg.) is then chromatographed on 140 g. of neutral silica gel, packed with 5 percent by volume ethyl acetate in hexane and eluted with 20 percent by volume ethyl acetate in hexane. Thereupon, 750 mg. of PGD_2, 1,15-lactone, 9-(tetrahydropyranyl ether) are obtained. Infrared absorptions are observed at 1745, 1460, 1440, 1370, 1340, 1240, 1200, 1160, 1140, 1120, 1080, 1040, 1020, 995, 980, 920, 870, 815, and 735 $cm.^{-1}$. NMR absorptions are observed at 5.90—5.0 and 4.80—3.40 δ.

(5) A mixture of 700 mg. of the reaction product of subpart (4) above, 33 ml. of tetrahydrofuran, 33 ml. of water, and 66 ml. of acetic acid is heated at 40°C. for 3 hr. The resulting mixture is then cooled to below room temperature, poured into a mixture of brine and water (1:1 v/v), and extracted thoroughly with a mixture of ethyl acetate and hexane (1:1 v/v). The combined organic extracts are then washed with aqueous sodium bicarbonate and brine, dried over sodium sulfate and evaporated. Crude product is then crystallized from diethyl ether and hexane

mixtures yielding 243 mg. of pure title product. Melting point 93—94°C. Infrared absorptions are observed at 3470, 3020, 1735, 1725, 1245, 1225, 1160, 1145, 1045, 1025, 960, and 917 $cm.^{-1}$. NMR absorptions are observed at 5.95—5.35, 5.4—4.95, 4.65—4.30, and 2.45 δ. The mass spectrum shows parent peak at 406.2574 and other peaks at 391, 388, 373, 335, 316, 290, and 279.

B. Employing $PGF_{2\alpha}$ as starting material:

(1) $PGF_{2\alpha}$ is selectively silylated at C—11 and C—15, preparing the formula XLII compound; etherified at C—9, preparing the formula XLV compound; and selectively desilylated at C—11 and C—15 forming a formula XLVI compound; following the procedures described in Example 13, part A, subparts (1), (2), and (3).

(2) The reaction product of subpart (1) above is then 1,15-lactonized following the procedure of Preparation 1, preparing a formula XLVII compound, $PGF_{2\alpha}$, 1,15-lactone, 9-(tetrahydropyranyl ether).

(3) The reaction product of subpart (2) above is oxidized to a ketone at C—11 and hydrolyzed at C—9, following the procedure of Example 13, part A, subparts (4) and (5), thereby preparing the title product.

Following the procedure of Example 13, part A, or Example 13, part B, but employing each of the various PGF_{α}-type, 1,15-lactones described following Preparation 2, or PGF_{α}-type compounds described by formula I, respectively, in place of $PGF_{2\alpha}$, 1,15-lactone or $PGF_{2\alpha}$, respectively, there are obtained each of the various corresponding PGD-type, 1,15-lactones.

Example 14.
8β,12α-PGD_2, 1,15-lactone

Refer to Chart D.

8β,12α-$PGF_{2\alpha}$, 1,15-lactone (Example 1) is selectively silylated at C—9, following the procedure of part A of Example 11 of Application No. 26180/76, (Serial No. 1554024), preparing a formula LXV compound.

B. This formula LXV compound is then oxidized at C—11, following the procedure of part B of Example 11 of Application No. 26180/76 (Serial No. 1554024), thereby preparing a formula LXXII PGD-type 9-trimethylsilyl ether.

C. Following the procedure of part C of Example 11 of Applicaion No. 26180/76 (Serial No. 1554024), the reaction product of part B above is hydrolyzed, thereby preparing the title product.

Following the procedure of Example 14, but employing each of the various 8β,12α-PGF_{α}-type, 1,15-lactones described following Example 1 in place of 8β,12α-$PGF_{2\alpha}$, 1,15-lactone, there are obtained each of the various corresponding 8β,12α-PGF_{α}-type, 1,15-lactones.

Example 15.
9β-PGD_2, 1,15-lactone

Refer to Chart G.

A. Following the procedure of part A of Example 11 of Application No. 26180/76 (Serial No. 1554024), PGE_2, 1,15-lactone is silylated at C—11, preparing a formula CLII compound.

B. Following the procedure of part B(4) of Example 12 of Application No. 26180/76 (Serial No. 1554024), the reaction product of part A above is reduced at C—9 and chromatographed yielding a 9β-hydroxy formula CLIII compound.

Following the procedure of Example 13, part A, subparts (2)—(5), the reaction product of part B above is etherified at C—9, thereby preparing the formula CLIV compound; selectively hydrolyzed at C—11 (silyl removal), preparing a formula CLV compound; oxidized at C—11, preparing a formula CLVI compound; and hydrolyzed at C—9, thereby preparing the title product.

Following the procedure of Example 15, but employing each of the various PGE-type, 1,15-lactones described following Example 2, in place of PGE_2, 1,15-lactone, there are obtained each of the various corresponding 9β-PGD-type, 1,15-lactones.

Example 16.
8β,9β,12α-PGD_2, 1,15-lactone

Refer to Chart G.

Following the procedure of Example 15, but employing 8β,12α-PGE_2, 1,15-lactone (Example 3) in place of PGE_2, 1,15-lactone, there is obtained the title product.

Following the procedure of Example 16, but employing each of the various 8β,12α-PGE-type, 1,15-lactones described following Example 3 in place of 8β,12α-PGE_2, 1,15-lactone, there are obtained each of the various corresponding 8β,9β,12α-PGD-type, 1,15-lactones.

Example 17.

9-Deoxy-9,10-didehydro-PGD_2, 1,15-lactone

Refer to Chart F.

Following the procedure of Example 10, PGD_2, 1,15-lactone is dehydrated, yielding the title compound.

Following the procedure of Example 17, but employing each of the various PGD-type, 1,15-lactones described following Example 13, or each of the various 9,10-didehydro-9-deoxy-PGD-type compounds described by formula I, there are prepared each of the various corresponding 9-deoxy-9,10-didehydro-PGD-type, 1,5-lactones.

Example 18.

9-Deoxy-9,10-didehydro-8β,12α-PGD_2

Refer to Chart F.

Following the procedure of Example 10 8β,12α-PGD_2 1,15-lactone is dehydrated, preparing the title compound.

Following the procedure of Example 18, but employing each of the various 8β,12α-PGD-type compounds described following Example 14 or 9-deoxy-9,10-didehydro-8β,12α-PGD-type compounds described by formula I, there are prepared each of the various corresponding 9-deoxy-9,10-didehydro-8β,12α-PGE-type, 1,15-lactones.

Example 19.

9-deoxy-PGD_2, 1,15-lactone

Refer to Chart H.

A. To a stirred solution of 9-deoxy-9,10-didehydro-PGD_2, 1,15-lactone dissolved in methanol at −25°C. under a nitrogen atmosphere, there is added a solution of sodium borohydride in water and methanol. This mixture is then stirred at −20°C. for 20 min. and thereafter a small quantity of acetic acid is added cautiously. The mixture is concentrated and an additional water is added and the pH of the mixture is thereafter adjusted to 3 by addition of citric acid. The resulting mixture is then extracted with dichloromethane and the combined organic extracts are washed with water and brine, dried and concentrated to yield the corresponding formula CLXXVII 9-deoxy-$PGF_{2\alpha}$, 1,15-lactone.

B. To a solution of the reaction product of part A dissolved in acetone at −20°C., there is added dropwise with stirring over one min. the Jones reagent. This resulting mixture is then stirred at −20°C. for an additional 20 min. and thereafter a small quantity of isopropanol is added. This mixture is then stirred for about 10 min. at −20°C. Thereafter the mixture is diluted with water and extracted with diethyl ether. Combined organic extracts are washed, dried, and concentrated. The resulting residue is then chromatographed on silica gel, yielding pure title product

Following the procedure of Example 39, but employing each of the various 9-deoxy-9,10-didehydro-PGD-type, 1,15-lactones described by formula CLXXVI in place of 9-deoxy-9,10-didehydro-PGD_2, 1,15-lactone there are obtained each of the various corresponding 9-deoxy-PGD-type, 1,15-lactones.

Example 20.

9-deoxy-8β,12α-PGD_2, 1,15-lactone

Refer to Chart G.

Following the procedure of Example 19, 9-deoxy-9,10-didehydro-8β,12α-PGD_2, 1,15-lactone is thereby transformed to the title product.

Following the procedure of Example 20, but employing each of the various 9-deoxy-9,10-didehydro-8β,12α-PGD-type, 1,15-lactones described following Example 19, there are obtained each of the various corresponding 9-deoxy-8β,12α-PGD_2-type, 1,15-lactones.

Example 21.

cis-4,5-Didehydro-$PGF_{1\alpha}$ 1,15-lactone

Refer to Chart D.

A. 200 mg. of *cis*-4,5-didehydro-$PGF_{1\alpha}$ and 65 mg. of n-butylboronic acid in 10 ml. of dichloromethane are reacted according to the procedure of Preparation 2, to give 340 mg. of an oil.

B. The oil is then dissolved in 6.5 ml. of oxygen-free xylene and 190 mg. of 2,2'-dipyridyl sulfide followed by addition of 223 mg. of triphenylphosphine. Thereafter, the reaction proceeds as is described in Preparation 2, parts B and C. Chromatography yields 80 mg. of pure product. Silica gel R_f is 0.35 and ethyl acetate. The mass spectrum shows base peak at 480.3069 and other peaks at 480, 465, 390, 364, 300, and 217. NMR absorptions are observed at 6.25—4.83, 4.30—3.80, and 2.90—0.65 δ.

Example 22.

13,14-didehydro-$PGF_{1\alpha}$, 1,15-lactone

Refer to Chart D.

Following the procedure of Example 21, 880 mg. of 13,14-Didehydro-$PGF_{1\alpha}$ is transformed to 80 mg. of the title product. Melting point is 75—76°C. Infrared absorptions are observed at 3500, 2950, 2250, 1740, 1455, 1370, 1235, 1040, 735 $cm.^{-1}$. NMR absorptions are observed at 5.58—5.20, 4.40—3.90, 3.53—0.60 δ.

Example 23.

13,14-Didehydro-$PGF_{2\alpha}$, 1,15-lactone

Refer to Chart D.

Following the procedure of Example 21, but employing 240 mg. of 13,14-didehydro-$PGF_{2\alpha}$, there is obtained 80 mg. of title product. R_f is 0.4 in diethyl ether. Infrared absorptions are observed at 3300, 2940, 1735, 1330, 1240, 1140, 1115, 1100, and 1040 $cm.^{-1}$. NMR absorptions are observed at 5.75—5.22, 4.38—4.03, and 2.93—0.72 δ.

Example 24.

17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$, 1,15-lactone

Refer to Chart D.

A. A solution of 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$, 776 mg.) and 1-butaneboronic acid (225 mg.) in 25 ml. of methylene chloride is heated at reflux. After 15 min. the methylene chloride is heated at reflux. After 15 min. the methylene chloride is allowed to distill off slowly. Fresh methylene chloride is added when the total volume is reduced to about one-half of the original volume. After 90 minutes, all of the methylene chloride is removed in vacuo to afford cyclic boronate of the staring prostaglandin.

B. The cyclic boronate is dissolved in 5 ml. of anhydrous, oxygen-free xylene and is treated with 2,2'-dipyridyl disulfide (660 mg.) and triphenylphosphine (786 mg.). After four hours at 25°C. the reaction mixture is diluted with 500 ml. of anhydrous, oxygen-free xylene and is heated at reflux for 18 hr. The xylene is removed *in vacuo* to give a residue. The residue is taken up in 50 ml. of tetrahydrofuran containing 1 ml. of 30 percent aqueous hydrogen peroxide (11.6 mmoles) and treated at 25°C. with a solution of sodium bicarbonate (1.68 g.) in 10 ml. of water. This mixture is stirred vigorously for 30 min., then concentrated under reduced pressure to give a residue. The residue is taken up in brine/ethyl acetate and extracted thoroughly with ethyl acetate. The combined extracts are washed with aqueous sodium bisulfate, water, aqueous sodium bicarbonate and brine, then dried over sodium sulfate and concentrated to afford a residue of crude 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$, 1,15-lactone.

The crude lactone is purified by chromatography on 400 g. of neutral silica packed and eluted (22 ml. fractions) with ethyl acetate. The fractions which contained the product, based on TLC, are yielding purified 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$, 1,15-lactone. The lactone crystallized upon trituration and after two recrystallizations from ethyl acetate/hexane exhibits m.p. 116—117°C.

The infrared spectrum exhibits peaks at 3460, 3400 sh, 3020, 1705, 1650, 1605, 1495, 1325, 1300, 1265, 1150, 1100, 1040, 1020, 1000, 970, and 700 $cm.^{-1}$ and the mass spectrum shows fragments at m/e 370 (M—18), 352, 334, 308, 298, 261, 243, 225. (No M+ peak is apparent).

Example 25.

17-Phenyl-18,19,20-trinor-PGE_2, 1,15-lactone

Refer to Chart E.

A solution of 17-phenyl-18,19,20-trinor-PGE_2 (735 mg.), 2,2'-dipyridyldisulfide (628 mg.) and triphenylphosphine (748 mg.) in 10 ml. of anhydrous, oxygen-free

xylene is stirred at 25°C. in an atmosphere of nitrogen for 2 hr. The mixture is then diluted with 400 ml. of anhydrous, oxygen-free xylene, heated at reflux for 2.5 hrs., and evaporated under vacuum at 30°C. to give a residue. The residue is chromatographed on 100 g. of neutral silica, packed and eluted (8 ml. fractions) with 80 percent by volume diethyl ether/hexane. The fractions containing homogeneous product by TLC are combined to afford purified 17-phenyl-18,19,20-trinor-PGE_2, 1,15-lactone. Two recrystallizations from diethyl ether/hexane afford pure product, m.p. 81—83°C. The infrared spectrum exhibits peaks at 3440, 3000, 1725, 1605, 1500, 1330, 1240, 1160, 1145, 1085, 1045, 975, 745, 725 and 700 $cm.^{-1}$ and the mass spectrum shows fragments at m/e 368 (M—18), 350, 332, 297, 296, 277, 264, 259, 241 (no M+ apparent).

Example 26.

16-Phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$, 1,15-lactone

Refer to Chart A.

Following the procedure of Preparation 1 but substituting 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$ for $PGF_{2\alpha}$ there is produced a crude product of 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$, 1,15-lactone as a viscous yellow oil.

The crude product is purified by chromatography over neutral silica packed in 50 percent by volume ethyl acetate/hexane and eluted with 50 percent by volume ethyl acetate/hexane followed by 70 percent by volume ethyl acetate/hexane. Those fractions containing homogeneous product as determined by TLC are combined to afford crystalline 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$, 1,15-lactone. The lactone thus obtained is recrystallized from ethyl acetate/hexane to afford pure product, m.p. 185—186°C. The mass spectrum of the trimethylsilyl derivative exhibits a peak at M + 516.2738 (theory for $C_{28}H_{44}Si_2O_5$: 516.2727) and fragments at m/e 501, 426, 423, 409, 400, 333, 307, 217 and 181.

Example 27.

$PGF_{1\alpha}$, 1,15-lactone or 15-*epi*-$PGF_{1\alpha}$, 1,15-lactone

Refer to Chart A.

Following the procedure of Preparation 1, but substituting $PGF_{1\alpha}$ for $PGF_{2\alpha}$ there is obtained a crude product containing $PGF_{1\alpha}$, 1,15-lactone as a viscous yellow oil.

The crude product is purified by chromatography on 700 g. of neutral silica, packed and eluted with 50 percent by volume ethyl acetate/hexane. The first 2 liters of eluate are discarded, after which 100 ml. fractions are collected.

A minor product eluted first from the column (fractions 14—19) which is homogeneous by TLC was combined to give 15-*epi*-$PGF_{1\alpha}$, 1,15-lactone [(15R)-$PGF_{2\alpha}$, 1,15-lactone]. The infrared spectrum exhibits peaks at 3450, 1730, 1585, 1250, 1100, 970 and 735 $cm.^{-1}$ and the NMR spectrum shows peak ($\delta^{CDCl_3}_{TMS}$) at 5.85—5.05 (vinyl and C—15; multiplet; 3H;, 4.25—3.85 (C*H*OH; multiplet; 2H) and 3.30 ppm (singlet, shifts downfield when sample is cooled; O*H*; 2H).

The major product, eluted later from the column (fractions 21—28), was combined to afford purified $PGF_{1\alpha}$, 1,15-lactone. The purified $PGF_{1\alpha}$, 1,15-lactone crystallizes upon trituration with diethyl ether, and recrystallization (ethyl acetate/hexane) affords a pure sample, m.p. 105—106°C. The infrared spectrum exhibits peaks at μmax 3520, 3480, 3380, 1710, 1300, 1290, 1265, 1250, 1235, 1160, 1110, 1075, 1055, 1000, and 965 $cm.^{-1}$. The NMR spectrum shows peaks at 6.0—5.75 (vinyl; multiplet; 2H; 5.60—5.00 (C—15H; multiplet; 1H), 4.25—3.80 (C*H*OH; multiplet; 2H) and 3.08 ppm (O*H*; singlet, shifts downfield on cooling; 2H), and the mass spectrum shows fragments at 338 (M+), 320, 302, 266, 249, 231.

Example 28.

PGE_1, 1,15-lactone

Refer to Chart C.

Following the procedure of Example 2, but substituting $PGF_{1\alpha}$, 1,15-lactone for $PGF_{2\alpha}$, 1,15-lactone, there is produced a crude product containing PGE_1, 1,15-lactone. Chromatography of the crude PGE_1, 1,15-lactone over neutral silica packed in 20 percent by volume ethyl acetate/hexane affords pure PGE_1, 1,15-lactone, m.p. 87—88°C.

The infrared spectrum exhibits peaks at 3390, 3320 sh, 1745, 1720, 1335, 1255, 1235, 1195, 1180, 1160, 1100, 1075, and 980 $cm.^{-1}$; the NMR spectrum exhibits peaks ($\delta^{CDCl_3}_{TMS}$) at 6.1—5.85 (vinyl; multiplet; 2H), 5.45—5.05 (C—15H; multiplet; 1H), and 4.40—3.85 ppm (C—11H; multiplet; 1H); and the mass spectrum of the

trimethylsilyl ether showed M+ 408.2694 (theory for $C_{23}H_{40}SiO_4 = 408.2696$) as well as peaks at m/e 393, 390, 380, 375, 365, 364, 318, 264, 150, and 99.

Example 29.
15-Methyl-$PGF_{2\alpha}$, 1,15-lactone

Refer to Chart D.

15-Methyl-$PGF_{2\alpha}$ (1.97 g.) is transformed by the procedure of Preparation, 2 part A, to a corresponding cycloboronate.

B. The reaction product of part A is then reacted with 40 ml. of xylene, 2.10 g. of triphenylphosphine, and 1.67 g. of 2,2'-dipyridyl disulfide, with stirring for 4 hr. at room temperature, thereby preparing the pyridine thiol ester of the reaction product of part A.

C. The reaction product of part B (about 40 ml.) is then divided into two equal volume aliquots which are separately lactonized as follows:

About one-half of the reaction product of part B (20 ml.) is then combined with 1 l. of oxygen-free xylene and heated at reflux for 7 hr. The resulting mixture is then cooled to room temperature and the xylene evaporated under reduced pressure.

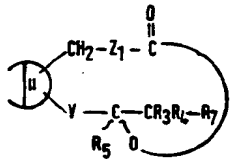
D. The reaction product of part C is then treated with 100 ml. of tetrahydrofuran, 2 ml. of hydrogen peroxide, and 20 ml. of saturated sodium bicarbonate. This mixture is then vigorously stirred at room temperature for 30 min., diluted with 50 ml. of water, and dried under reduced pressure. The residue is then diluted with brine, extracted with ethyl acetate, and the organic layer washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure, yielding a 3.2 g. residue. This residue is then chromatographed on 150 g. of silic gel, packed with 50 percent by volume ethyl acetate in hexane, eluting with 50 to 100 percent by volume ethyl acetate in hexane and thereafter with 20 percent by volume methanol in ethyl acetate. Fractions containing pure title product are combined, yielding 8.5 mg. The mass spectrum of the bis TMS derivative shows a parent peak at 494.3234 and other peaks at 479, 450, 423, 404, 378, 367, 314, 351 and 217.

Preferred compounds of the invention whose preparation is not exemplified above are the 1,15-lactones of 2a,2b-dihomo-15-methyl-$PGF_{2\alpha}$; 15-methyl-16,16-difluoro-$PGF_{2\alpha}$; 15,16,16-trimethyl-$PGF_{2\alpha}$; 16,16-difluoro-$PGF_{2\alpha}$; 16,16-dimethyl-$PGF_{2\alpha}$; 2a,2b-dihomo-9,10-didehydro-9-deoxy-PGE_2; 15-methyl-16,16-difluoro-9,10-didehydro-9-deoxy-PGD_2; 15,16,16-trimethyl-9,10-didehydro-9-deoxy-PGD_2; 15-methyl-9,10-didehydro-9-deoxy-PGD_2; 16,16-difluoro-9,10-didehydro-9-deoxy-PGD_2; and 16,16-dimethyl-9,10-didehydro-9-deoxy-PGD_2.

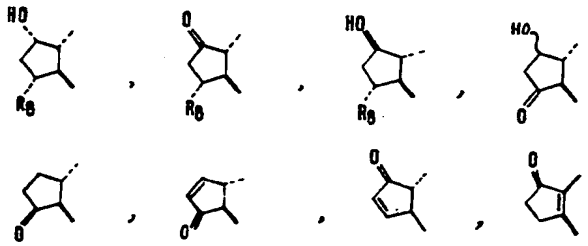
We make no claim herein in the compound $PGF_{2\alpha}$ 1,15-lactone or to pharmaceutical compositions containing the compound. Such compositions are described and claimed in Application No. 26181/76 (Serial No. 1554023). Subject to the foregoing disclaimer.

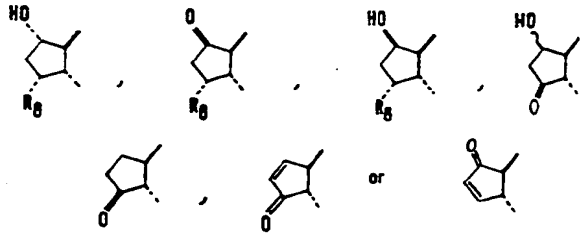
WHAT WE CLAIM IS:—

1. A prostaglandin 1,15-lactone of the formula

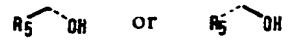


wherein (II) is

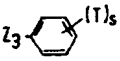




wherein R_8 is hydroxy;
wherein R_3 and R_4 are the same or different and are each hydrogen, methyl or fluorine, with the proviso that CR_3R_4 is not CFMe;
wherein M_1 is



wherein R_5 is hydrogen or methyl;
wherein R_7 is $-(CH_2)_m-CH_3$, wherein m is an integer of from one to 5, *cis*-$CH=CH-CH_2CH_3$, or an optionally substituted phenoxy or benzyl radical of the formula



wherein Z_3 is —O— or $-CH_2-$, T is chlorine, fluorine, trifluoromethyl or alkyl or alkoxy of one to 3 carbon atoms, s is zero, one, 2 or 3, with the provisos that when s is 2 or 3 the T's may be the same or different, that not more than two T's are other than alkyl, and that Z_3 is not —O— when either or both of R_3 and R_4 is fluorine;
wherein Y_1 is *trans*-$CH=CH-$, $-CH_2CH_2-$, *cis*-$CH=CH-$ or $-C\equiv C-$;
wherein ~ indicates attachment of the hydroxy group to the cyclopentane ring or of the C—15 substituents in either alpha or beta configuration; and
wherein Z_1 is
(1) *cis*-$CH=CH-CH_2-(CH_2)_g-CH_2-$,
(2) *cis*-$CH=CH-CH_2-(CH_2)_g-CF_2-$,
(3) *cis*-$CH_2-CH=CH-(CH_2)_g-CH_2-$,
(4) $-(CH_2)_3-(CH_2)_g-CH_2-$,
(5) $-(CH_2)_3-(CH_2)_g-CF_2-$,
(6) $-CH_2-O-CH_2-(CH_2)_g-CH_2-$,
(7) $-L-O-(CH_2)_g-$ or
(8) $-L-CH_2-(CH_2)_g$
wherein L is 1,3-phenylene and g is one, 2 or 3.

2. A compound as claimed in claim 1 wherein R_7 is *cis*—$CH=CH-CH_2CH_3$.

3. A compound as claimed in claim 1 wherein R_7 is optionally substituted benzyl as defined in claim 1.

4. A compound as claimed in claim 1 wherein R_7 is optionally substituted phenoxy as defined in claim 1.

5. A compound as claimed in claim 1 wherein R_7 is $-(CH_2)_m-CH_3$ wherein m is as defined in claim 1.

6. A compound as claimed in claim 5 wherein m is 3.

7. A compound as claimed in any preceding claim wherein Y_1 is $-C\equiv C-$.

8. A compound as claimed in any of claims 1 to 6 wherein Y_1 is *cis*—$CH=CH-$.

9. A compound as claimed in any of claims 1 to 6 wherein Y_1 is $-CH_2CH_2-$.

10. A compound as claimed in any of claims 1 to 6 wherein Y_1 is *trans*-$CH=CH-$.

11. A compound as claimed in any preceding claim wherein Z_1 is *cis*-$CH=CH-CH_2(CH_2)_g-CF_2-$ wherein g is as defined in claim 1.

12. A compound as claimed in any of claims 1 to 10 wherein Z_1 is $-(CH_2)_3-(CH_2)_g-CF_2-$ wherein g is as defined in claim 1.

13. A compound as claimed in any of claims 1 to 10 wherein Z_1 is $-(CH_2)_2-O-(CH_2)_g-CH_2-$ wherein g is as defined in claim 1.

14. A compound as claimed in any of claims 1 to 10 wherein Z_1 is *cis*-$CH_2-CH=CH-(CH_2)_g-CH_2-$ wherein g is as defined in claim 1.

15. A compound as claimed in any of claims 1 to 10 wherein Z_1 is

$-(CH_2)_3-(CH_2)_g-CH_2-$ wherein g is as defined in claim 1.

16. A compound as claimed in any of claims 1 to 10 wherein Z_1 is $-L-CH_2-(CH_2)_g-$ wherein L and g are as defined in claim 1.

17. A compound as claimed in any of claims 1 to 10 wherein Z_1 is $-L-O-(CH_2)_g-$ wherein L and g are as defined in claim 1.

18. A compound as claimed in any of claims 1 to 10 wherein Z_1 is *cis*$-CH=CH-(CH_2)_g-CH_2-$ wherein g is as defined in claim 1.

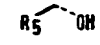
19. A compound as claimed in any of claims 11 to 18 wherein g is 3.

20. A compound as claimed in any of claims 11 to 18 wherein g is one.

21. A compound as claimed in any preceding claim wherein M_1 is

wherein R_5 is as defined in claim 1.

22. A compound as claimed in any of claims 1 to 18 wherein M_1 is



wherein R_5 is as defined in claim 1.

23. A compound as claimed in any preceding claim wherein R_5 is methyl.

24. A compound as claimed in any of claims 1 to 22 wherein R_5 is hydrogen.

25. A compound as claimed in any preceding claim wherein at least one of R_3 and R_4 is fluorine.

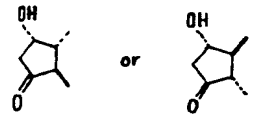
26. A compound as claimed in claim 25 wherein R_3 and R_4 are both fluorine.

27. A compound as claimed in any of claims 1 to 24 wherein at least one of R_3 and R_4 is methyl.

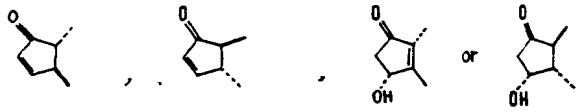
28. A compound as claimed in claim 27 wherein R_3 and R_4 are both methyl.

29. A compound as claimed in any of claims 1 to 24 wherein R_3 and R_4 are both hydrogen.

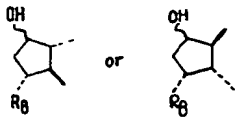
30. A compound as claimed in any preceding claim wherein (ii) is



31. A compound as claimed in any of claims 1 to 29 wherein (ii) is



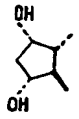
32. A compound as claimed in any of claims 1 to 29 wherein (ii) is



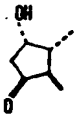
wherein R_8 and ~ are as defined in claim 1.

33. A compound as claimed in any of claims 1 to 29 wherein (ii) is

34. A compound as claimed in any of claims 1 to 29 wherein (III) is



35. A compound as claimed in any of claims 1 to 29 wherein (III) is



36. A compound as claimed in any of claims 1 to 29 wherein (III) is

37. A compound as claimed in any of claims 1 to 29 wherein (III) is

38. A compound as claimed in any of claims 1 to 29 wherein (III) is

39. 2a,2b-Dihomo-15-methyl-$PGF_{2\alpha}$ 1,15-lactone.
40. 2a,2b-Dihomo-$PGF_{2\alpha}$ 1,15-lactone.
41. 15-Methyl-16,16-difluoro-$PGF_{2\alpha}$ 1,15-lactone.
42. 15,16,16-Trimethyl-$PGF_{2\alpha}$ 1,15-lactone.
43. 15-Methyl-$PGF_{2\alpha}$ 1,15-lactone.
44. 16,16-Difluoro-$PGF_{2\alpha}$ 1,15-lactone.
45. 16,16-Dimethyl-$PGF_{2\alpha}$, 1,15-lactone.
46. 2a,2b-Dihomo-9,10-didehydro-9-deoxy-PGD_2, 1,15-lactone.
47. 2a,2b-Dihomo-9,10-didehydro-9-deoxy-15-methyl-PGD_2, 1,15-lactone.
48. 15-Methyl-16,16-difluoro-9,10-didehydro-9-deoxy-PGD_2, 1,15-lactone.
49. 15,16,16-Trimethyl-9,10-didehydro-9-deoxy-PGD_2, 1,15-lactone.
50. 15-Methyl-9,10-didehydro-9-deoxy-PGD_2, 1,15-lactone.
51. 16,16-Difluoro-9,10-didehydro-9-deoxy-PGD_2, 1,15-lactone.
52. 16,16-Dimethyl-9,10-didehydro-9-deoxy-PGD_2, 1,15-lactone.
53. 9,10-Didehydro-9-deoxy-PGD_2, 1,15-lactone.

54. A process for the preparation of a lactone as claimed in claim 1 substantially as herein described with reference to any of the Examples.

55. A pharmaceutical composition comprising a lactone as claimed in any of claims 1 to 53 in association with a pharmaceutically acceptable carrier.

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